Signaling via Alk5 controls the ontogeny of lung Clara cells.

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Public Summary:

Scientific Abstract:
Clara cells, together with ciliated and pulmonary neuroendocrine cells, make up the epithelium of the bronchioles along the conducting airways. Clara cells are also known as progenitor or stem cells during lung regeneration after injury. The mechanisms of Clara cell differentiation are largely unknown. Transforming growth factor beta (TGFbeta)is a multifunctional molecule with roles in normal development and disease pathogenesis. In this study, we deleted the TGFbeta type I receptor Alk5 in the embryonic lung epithelium using Gata5-Cre mice. Absence of Alk5 blocked Clara cell differentiation but had no effect on ciliated or pulmonary neuroendocrine cells. Hairy/Enhancer of Split-1, which is expressed in Clara cell putative ;progenitors' was found to be a downstream target of Alk5 in vivo and in vitro. Loss of Alk5-mediated signaling also stimulated Pten gene expression and inhibited ERK phosphorylation in vivo. Using lung epithelial cells, we show that Alk5-regulated Hes1 expression is stimulated through Pten and the MEK/ERK and PI3K/AKT pathways. Thus, the signaling pathway by which TGFbeta/ALK5 regulates Clara cell differentiation may entail inhibition of Pten expression, which in turn activates ERK and AKT phosphorylation.